The Journal of Immunology

In This Issue

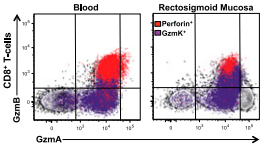
J Immunol 2018; 200:1531-1532; ;
doi: 10.4049/jimmunol.1890001
http://www.jimmunol.org/content/200/5/1531

The Journal of Immunology is published twice each month by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

Print ISSN: 0022-1767 Online ISSN: 1550-6606.

The Journal of Immunology

Peculiar Function of Rectosigmoid CD8$^+$ T Cells in HIV

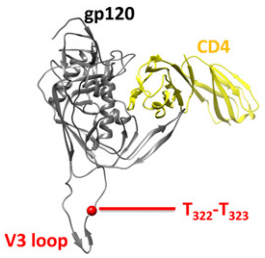


The gastrointestinal mucosa is a major site of HIV transmission. Mucosal CD8$^+$ T cells are thought to play a critical role in containing HIV-1 infection, but the profiles of cytotoxic effector molecules in CD8$^+$ T cells during HIV infection have not been delineated. To assess this, Kiniry et al. (p. 1876) used blood and rectosigmoid mucosal biopsies from HIV-1 patients and seronegative (SN) controls to define the expression patterns of the cytolytic effector molecules perforin and granzymes (Gzms) A, B, and K and identified a novel subset of mucosal CD8$^+$ T cells highly expressing GzmA. Perforin$^+$GzmA^{Int}GzmB$^+$ CD8$^+$ T cells were significantly higher in the blood compared with the mucosa, but the mucosa contained a significantly higher percentage of perforin- and GzmB-negative GzmA^{Int} CD8$^+$ T cells, both in HIV patients and in SN controls. In the mucosa of HIV-1 patients, the proportion of GzmB-expressing but perforin-negative CD8$^+$ T cells was significantly greater in response to stimulation with HIV Gag, compared with *Staphylococcal* enterotoxin B (SEB). Furthermore, GzmA$^+$GzmB$^+$GzmK$^+$ cells constituted a larger proportion of Gag-responsive CD8$^+$ T cells, compared with SEB-responsive CD8$^+$ T cells in the mucosa, but not the blood. However, in response to Gag and SEB stimulation, a greater proportion of rectosigmoid CD8$^+$ T cells did not express any cytotoxic effectors, compared with blood. Overall, rectosigmoid CD8$^+$ T cells appeared to be able to generate cytokines, rather than mediate cytotoxic responses. Mucosal GzmA$^+$ CD8$^+$ T cells were predominantly effector memory cells, suggesting that GzmA^{Bright} CD8$^+$ T cells are tissue-resident CD8$^+$ T cells unique to the mucosa. Taken together, these data demonstrate that rectosigmoid CD8$^+$ T cells in HIV-1 patients produce Gzms independently of perforin, which may enable them to use Gzms for noncytolytic functions and mediate proinflammatory responses rather than direct cytotoxicity.

IL-10 Takes On Proinflammatory Role To Promote Autoimmune Neuropathy

Chronic inflammatory demyelinating polyneuropathy, an acquired autoimmune demyelination of peripheral nerves, is associated with increased IL-10, but this cytokine's role in pathogenesis remains unclear. In this issue, Smith et al. (p. 1580) demonstrated increased IL-10 expression in sciatic nerves of *NOD.Aire*$^{GW/+}$ (*Aire*$^{GW/+}$) mice, which develop spontaneous autoimmune peripheral polyneuropathy (SAPP), compared with NOD wild-type (WT) controls. Surprisingly, IL-10 deficiency protected *Aire*$^{GW/+}$ animals against the development of SAPP, nerve infiltration of inflammatory cells, and electrophysiological changes in the peripheral nerves consistent with demyelination, suggesting a pathogenic role for IL-10 in SAPP. IL-10 expression was significantly increased in CD4$^+$ T cells from the spleen and nerve-draining lymph nodes (LN) of *Aire*$^{GW/+}$ mice compared with WT controls. Consistent with these observations, transfer of IL-10–deficient CD4$^+$ T cells from *Aire*$^{GW/+}$ mice into both IL-10–sufficient and IL-10–deficient *NOD*.Prkdc$^{Scid/Scid}$ mice induced SAPP, but disease progression was delayed and the pathology less severe in animals receiving IL-10–deficient compared with IL-10–sufficient CD4$^+$ T cells. IL-10 deficiency in *Aire*$^{GW/+}$ mice was also associated with an increased frequency of highly activated CD4$^+$ T cells in the spleen and LN, and enlarged nerve-draining LN that, on average, contained three-fold more cells than LN of both WT and IL-10 sufficient *Aire*$^{GW/+}$ mice. Cells from the enlarged LN of IL-10–deficient *Aire*$^{GW/+}$ mice were less migratory toward increasing sphingosine-1-phosphate (S1P) gradients in vitro, and CD4$^+$ T cells from these mice expressed significantly reduced levels of S1P receptor 1 (S1PR1), relative to IL-10–sufficient controls, a reduction that was STAT3 dependent. Finally, blockade of S1PR1 activity prevented SAPP development in *Aire*$^{GW/+}$ mice. Therefore, these data support a model in which IL-10-induced STAT3 upregulates S1PR1 expression on CD4$^+$ T cells to enhance their migration into the peripheral nervous system and promote SAPP development. These findings suggest that treatment of autoimmune and inflammatory diseases with IL-10 may have previously unanticipated effects.

A Novel HIV Strategy To Avoid Cross-Presentation



During infection with HIV, viral Ags are taken up and processed in the endosomes of DCs and cross-presented on MHC class I (MHC-I) molecules to CD8$^+$ T cells. Cathepsin S, a protease that was recently demonstrated to be important for cross-presentation, has cleavage sites that are highly conserved among many HIV glycoprotein gp120 isolates, even though they are in regions that have high mutation rates. In this issue, Frey et al. (p. 1853) investigated the role of cross-presentation in inducing HIV-specific CD8$^+$ T cell responses by engineering a gp120 variant resistant to cathepsin S digestion via mutation of the cleavage site $T_{322}T_{323}$ to $V_{322}V_{323}$ in the V3 domain (VV gp120). Splenocytes from mice immunized with whole VV gp120 had a greater IFN-γ^+ CD8$^+$ T cell response after stimulation with peptides spanning the wild-type (WT) HIV gp120 than did mice immunized with the WT gp120 protein. Epitope mapping revealed that CD8$^+$ T cell responses in

immunized mice were primarily directed to a previously described immunodominant epitope, IGPGRAFYTT (s.p.TT10), located in the V3 domain that also includes the mutated cathepsin S site. Peptide–MHC binding assays demonstrated that peptides containing the s.p.TT10 epitope were bound and presented by the MHC-I molecule H2-D^d, but that mutation in the cathepsin S cleavage site (s.p.VV) did not improve epitope affinity for MHC-I. Rather, X-ray crystallographic studies demonstrated that the increased $CD8^+$ T cell responses to the VV mutation are likely attributed to elimination of the cathepsin S cleavage site and therefore protection of gp120 from endosomal cross-presentation. In support of these observations, when WT HIV proteins containing the epitope s.p.TT10 were expressed in a vaccinia virus, the WT protein elicited a strong IFN-γ^+CD8^+ T cell response as vaccinia expresses the protein in the cytosol, thereby obviating the need for passage through the endosomes. Therefore, this study demonstrates that a virus such as HIV, which infects primarily nonprofessional Ag presenting cells, can escape T cell recognition by incorporating a cathepsin S cleavage site in an immunodominant epitope that is then destroyed when the Ag undergoes endosomal cross-presentation. Recognition of this evasion strategy may facilitate the development of more effective HIV vaccine candidates.

Role of Copper in Inflammasome Activation

The NLRP3 inflammasomes are activated by diverse pathogen- and host-derived factors, but regulation of the NRLP3 inflammasome by redox mechanisms remains unknown. Specifically, the role of copper in inflammasome activation has not been assessed. In this issue, Deigendesch et al. (p. 1607) investigated the effects of copper availability on inflammasome activation in macrophages and monocytes by using the copper chelator tetrathiomolybdate (TTM) and examining activation of inflammasomes, downstream inflammatory mediators such as IL-1β, and copper- and zinc-dependent superoxide dismutase 1 (SOD1). In a mouse model of acute inflammation, TTM treatment decreased serum caspase-1–dependent cytokines, such as IL-1β, and markers of sepsis. In vitro, TTM inhibited IL-1β release from bone marrow–derived macrophages in a dose-dependent manner following canonical NLRP3, but not noncanonical, inflammasome activation. To further investigate the copper-dependent mechanisms of NLRP3 activation, the authors used SOD1-deficient peritoneal macrophages (PMs) and found that copper depletion did not affect residual activation of caspase-1 in these cells, suggesting that TTM reduces caspase-1 activation by inhibiting SOD1 in macrophages. TTM treatment did not affect secretion of IL-1β from human blood–derived $CD14^{high}$ monocytes, but reduced the secretion of IL-1β from human PMs isolated from ascites. These data indicate that SOD1 regulates NLRP3 activation in macrophages but not monocytes and reveal a novel role of copper in canonical NLRP3 activation in macrophages. The findings provide preclinical support for the use of TTM, a currently approved drug, in the treatment of chronic inflammation.